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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MYERS, CARLA J

ART UNIT	PAPER NUMBER
1634	16

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/824,629	LENZ ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-31* is/are pending in the application.

4a) Of the above claim(s) *1-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to Paper No. 15, filed September 16, 2002. Applicants arguments presented in the response of Paper No. 16 have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. This application contains claims 1-12 drawn to an invention nonelected with traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. Claims 14-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying increased risk of colon cancer in Hispanic subjects under the age of 35 wherein the methods comprise analyzing the nucleic acid of said subject and detecting the presence of a polymorphism in the MnSOD gene at the position encoding amino acid -9 of the MnSOD signal peptide, wherein when said subject is identified as being at increased risk of developing colon cancer when said subject is homozygous for the C allele at the nucleotide position encoding amino acid -9 of the MnSOD signal peptide, does not reasonably provide enablement for methods wherein any other alleles of the MnSOD gene are analyzed, methods wherein non-humans are diagnosed, or methods in which the subjects is not Hispanic or is over 35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 14-31 are drawn to methods for diagnosing colon cancer comprising detecting the presence of a mutation in a first and second allele of the MnSOD gene wherein the mutation is in the coding region for the MTS of the MnSOD protein and results in a loss of alpha-helical structure . The claims further include methods in which a region of the MnSOD gene including nucleotide 351 of SEQ ID NO: 1 is analyzed. The specification (see, for example, table 1) teaches only a single polymorphism in the gene encoding MnSOD, i.e. the mutation of a T to C at the nucleotide position encoding amino acid -9 of the MnSOD signal peptide, which corresponds to position 351 within the MnSOD fragment of SEQ ID NO: 1 and which results in a Val to Ala substitution in the MnSOD signal peptide. The specification teaches that in a sample population of Hispanics, the C/C genotype was present in 38% of controls and in 38% of colon cancer patients; the C/T genotype was present in 48% of the controls and 45% of colon cancer patients; and the T/T genotype was present in 14% of controls and 17% of colon cancer patients. Accordingly, the results provided in the specification clearly teach that detection of the alteration of the MnSOD gene encoding amino acid -9 of the MnSOD signal peptide cannot be used to diagnose colon cancer in the general population since the mutation occurs at equal frequency in the control population and colon cancer patients. The specification further states that there is an association between risk of colon cancer and the stated mutation of the MnSOD gene in Hispanic individuals under the age of 35. In particular, the C/C genotype was found in 60% of colon cancer patients below the age of 35 and in 32% of colon cancer patients above the age of 35; the T/C and T/T genotypes together were present in 40% of the colon cancer patients below the age

of 35 and in 68% of the colon cancer patients above the age of 35. Accordingly, the specification has enabled methods for identifying increased risk of colon cancer in Hispanic subjects under the age of 35 wherein the methods comprise analyzing the nucleic acid of said subject and detecting the presence of a polymorphism in the MnSOD nucleic acid encoding amino acid position -9 of the MnSOD signal peptide wherein when said subject is identified as being at increased risk of developing colon cancer when said subject is homozygous for the C allele. However, the specification has not enabled methods in which the presence of a C at position 351 of SEQ ID NO: 1 of the MnSOD gene is indicative of increased risk of colon cancer because no data is provided for the individual frequencies of the T/C versus T/T genotypes and there is no evidence to support the allegation that individuals heterozygous for the C allele are at an increased risk for having or developing colon cancer. In addition, the specification provides no evidence on the frequency of this MnSOD mutation in the general population. Given the unpredictability in the art of genetic diagnosis, one cannot extrapolate the findings obtained with a single ethnic group to the general population. In addition, the specification is not enabling for the detection of any additional mutations or polymorphisms in the MnSOD gene. The specification has taught a single mutation in the MnSOD gene, i.e. the alteration resulting in a Val to Ala substitution at amino acid position -9 in the signal peptide sequence of the MnSOD protein. The prior art of St. Claire teaches 3 polymorphisms in the promoter region of the MnSOD gene. The specification provides no guidance as to how to predictably identify additional polymorphisms in the MnSOD gene that would be expected to be associated with colon cancer. The ability to establish a

correlation between the presence of a polymorphism and the occurrence of a specific disease is highly unpredictable and can only be determined through extensive, random, trial and error experimentation. The specification provides no guidance as to how to apply the claimed method of diagnosis to the general population, to individuals above the age of 35 or to non-human subjects and provides no guidance as to how to practice the invention by detecting uncharacterized alterations in the MnSOD gene. As stated in *Vaek* (20 USPQ2d 1438), the "specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, one cannot readily anticipate what additional polymorphisms may exist in the MnSOD gene which could be used to diagnose colon cancer and one cannot extrapolate the findings associated with a single polymorphism to other polymorphisms or to the general population. While one could contemplate a nucleotide substitution at each and every position in the MnSOD gene, such substitutions are not considered

to be equivalent to specific polymorphisms associated with risk of colon cancer. Polymorphisms in the MnSOD gene associated with colon cancer represent a distinct group of nucleotide variations which are expected to occur at only specific locations within the gene and consist of specific nucleotide alterations. Accordingly, knowledge of the sequence of the wild-type MnSOD gene does not allow the skilled artisan to envision all of the contemplated polymorphisms encompassed by the claimed genus. It is highly unpredictable as to which if any additional alterations in the MnSOD gene could be used to diagnose colon cancer. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

RESPONSE TO ARGUMENTS:

In the response of Paper No. 11, Applicants traverse this rejection by stating that Applicants are entitled to the full scope of the claimed invention because Applicants have demonstrated that a mutation that disrupts the MTS of MnSOD, inhibiting its import into the mitochondrion, leads to a dose dependent effect on the relative risk of early onset colorectal cancer. This argument is not convincing because the specification has established only that the mutation at position 351 of the MnSOD gene is correlated with the onset of colorectal cancer in Hispanic individuals under the age of 35. The specification has not established the broader concept that early onset of colorectal cancer is associated with any mutation in the MTS of the MnSOD that disrupts the alpha-helical structure of the MTS. There are no showings in the

specification that the loss of the alpha-helical structure of the MTS is important to the early onset of colorectal cancer. As discussed in the specification, the 351 mutation is not associated with the occurrence of colorectal cancer in general. The specification does not clarify why loss of the alpha-helical structure of the MTS predisposes individuals to early onset colorectal cancer and not to colorectal cancer in general. In the Shimoda-Matsubayashi reference (reference "C4" cited in the IDS of July 22, 2002 and addressed in the response of Paper No. 11), the authors establish an association between the 351 mutation (referred to therein as the -9Ala mutation) and the occurrence of Parkinson's disease. While the reference teaches that the 351 mutation results in disruption of the alpha-helical structure of the MTS of the MnSOD gene, the association between the 351 mutation and Parkinson's disease "may not be functional but due to the presence of linkage disequilibrium between the -9Ala allele in Parkisonian patients and a genetic variation increasing the risk of Parkinson's disease" (see page 565). In a post filing date reference published by Applicants (Stoehlmacher et al (2002); reference "C7" cited in the IDS of July 22, 2002), it is stated that "(t)he alanine allele was more frequently detected among young Hispanic individuals with colorectal cancer. The reason for this association is unclear." Thus, it is clear that while an association has been established between the 351 mutation and early onset of colorectal cancer in Hispanics, a more general association between mutations that disrupt the alpha-helical structure of the MTS and early onset colorectal cancer has not been established.

Applicants further traverse this rejection by stating that there is no evidence that the mitochondria of Hispanic persons function differently than those of any other group. Applicants

assert that "Given the straightforward nature of the relationship between mutations affecting the function of the protein and increased cellular damage by superoxide radical, there is no plausible scientific evidence to support any assertion that Hispanics differ from the other groups in this conserved function." Applicants arguments have been fully considered but are not convincing because they are based on the premise that the specification has in fact established an association between the loss of alpha-helical structure in the MTS and the occurrence of early onset colorectal cancer. However, Applicants have **not** established such an association. Applicants comments do not accurately characterize the information provided in the specification. A straightforward relationship between loss of the alpha-helical structure of the MTS and onset of colorectal cancer has not been disclosed. It is well accepted in the art that while an association between a polymorphism or mutations and the occurrence of a disorder may exist in one population, the same association may not be relevant in the general population. In Applicants own journal article (see page 238 of reference "C3"), Applicants state that "**An association between MnSOD genotype and age was not observed among non-Hispanic colorectal cancer patients.** This might be due in part to the small number of patients studied, which is not efficient to detect slight differences. However, there is evidence in the literature that Minority Americans including Hispanics are significantly earlier diagnosed with colorectal cancer than non-Hispanic white Americans. A larger study is needed to evaluate whether the -9Ala variant of the MnSOD gene contributes to this phenomenon." It is unclear as to how Applicants can on the one hand argue that any group of subjects having a mutation that disrupts the α-helical

structure of the MTS have an increased risk of early onset colorectal cancer, yet on the other hand, Applicants clearly state in their published paper than association has not been established between the 351 mutation and early onset colorectal cancer in non-Hispanics and that further research is required to determine if such an association exists.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

4. Claims 14-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A. The specification as originally filed does not provide basis for the concept of "assigning an intermediate risk of developing early onset colorectal cancer to a subject having a mutation in only one of the first and second allele of the MnSOD gene." While the specification (pages 20 and 34) discloses the concept that individuals homozygous for a C at position 351 of the MnSOD gene have an increased risk of developing colorectal cancer, the specification does not disclose the concept that individuals heterozygous for the 351 mutation have in intermediate risk of developing colorectal cancer. The specification (Table 2) analyzes individuals who are heterozygous (C/T) and homozygous for the T allele together and does not disclose a difference in the risk factor for developing colorectal cancer between heterozygous C/T individuals and homozygous T/T individuals.

B. The specification as originally filed does not provide support for the concept of determining whether an individual has a increased risk for developing **early onset colorectal cancer**. While the specification (page 34) states that a "T to C substitution in both alleles of the MnSOD gene increases the risk for colorectal cancer in young patients," the specification does not disclose the concept of determining the risk of early onset colorectal cancer. The risk of developing colorectal cancer in young patients is not equivalent to the risk of developing early onset colorectal cancer. There is no disclosure in the specification as originally filed to support the amendment to the claims to recite methods for determining the relative risk of developing early onset colorectal cancer.

5. Claims 27-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 is indefinite and vague over the recitation of "the identity of said genomic DNA at said position 351 can be determined" because it is not clear as to whether the method does in fact actual include a step of determining the nucleotide identity at position 351 and it is unclear as to how this step of identifying the nucleotide relates to the remainder of the claim. That is, does one assign a lower, intermediate or higher risk based on the presence or absence of the nucleotide at position 351 in one or both of the alleles?

Claims 28-30 are indefinite because it is unclear as to whether the recitation of "the mutation" in claim 28 refers back to the mutation in the first allele or the mutation in the second

allele or to both the mutation in the first and second allele. That is, it is unclear as to whether the method defines the mutation as it relates to only one of the alleles that are detected or if the method detects the presence or absence of the C at position 351 of the MnSOD gene in both the first and second allele.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-872-9306 or (703)-872-9307 (After final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703)308-0196.

Carla Myers

November 18, 2002

CARLA J. MYERS
PRIMARY EXAMINER